Chimeric antigen receptor (CAR) T-cell treatment for mantle cell lymphoma (MCL)

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Abstract: Mantle cell lymphoma (MCL) is a rare B-cell malignancy that remains challenging to treat with high rates of relapse. Frontline strategies range from intensive chemotherapy followed by consolidation with autologous stem cell transplant (ASCT), to less-intensive therapies including combination regimens. The treatment landscape for relapsed patients includes Bruton tyrosine kinase (BTK) inhibitors among other targeted treatments. Novel agents such as the selective BCL2 inhibitor venetoclax showed high response rates when used as monotherapy for refractory relapsed MCL. The rituximab, bendamustine, and cytarabine (R-BAC) regimen, while response rates were high, were not durable. Chimeric antigen receptor (CAR) T-cell products targeting CD19 have been efficacious in relapsed and refractory MCL patients. Brexucabtagene autoleucel (brexu-cel, formerly KTE-X19) was approved by US Food and Drug Administration (FDA) in July, 2020, for treatment of refractory and relapsed MCL. This article provides an overview for the available management strategies for relapsed MCL and examines the role of CAR T-cell in the current and future treatment of MCL.

Keywords: Brexu-cel, CAR-T, mantle cell lymphoma, KTE-X19, relapsed, ZUMA-2

Introduction

Mantle cell lymphoma (MCL) is a rare subtype of B-cell lymphoma that presents with a highly variable course. MCL is a neoplasm of mature B lymphocytes, expressing mature B-cell antigens (CD19, CD20, and CD22) and IgM and IgD surface immunoglobulins, as well as aberrant expression of CD5. The hallmark chromosomal translocation $t(11;14)(q13: q32)$, which results in overexpression of cyclin D1 (CCND1/PRAD-1 gene), is present in most cases. A cell cycle regulator, cyclin D1 is not expressed in normal B lymphocytes, rendering it a biomarker for pathologies with malignant B lymphocytes, including MCL. The overproduction of this oncogene leads to dysregulation of the cell cycle but does not represent the sole culprit of the pathogenesis of MCL. Rather, secondary oncogenic mechanisms, such as mutations that lead to dampened DNA damage response mechanisms, are required for MCL development.[1]

Clinically, MCL has a male predominance of 2:1, with a median age of 67 at diagnosis.[2] Factors predictive of poor outcome include advanced age, male sex, blastoid variant, advanced stage, extensive nodal involvement, high serum lactate dehydrogenase (LDH) level, and prognostic biomarkers such as high Ki-67 expression index and presence of *TP53* mutation.[3–6]

Despite advances in our understanding of the pathogenesis of MCL and approaches to management, this lymphoma remains incurable. Novel agents such as Bruton tyrosine kinase (BTK) inhibitors, lenalidomide, and venetoclax are effective but duration of response remains limited, and patients eventually relapse.[7–12] High-risk patients such as those with *TP53* aberrations, high Ki-67 or progression following BTK inhibition are a therapeutic challenge and novel agents are needed.

Chimeric antigen receptor (CAR) T-cell therapies targeting B-cell antigens have demonstrated considerable efficacy in both B-cell leukemia and lymphomas including MCL.[13–17] Given the substantial responses achieved in other B-cell malignancies, targeting cell surface B-cell antigens is a

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Table 1. Intensive therapy regimens of MCL.

Trial, regimen		ORR/CR	OS rate	PFS	MRD negativity[1]
Nordic lymphoma group[20]	Maxi-CHOP HiDAC	96%/54%	70% (6 years)	66% (6 years)	88% (36/42)
MCL younger[19]	R-CHOP/R-DHAP + HiDAC	95%/61%	75% (5 years)	N/A	N/A
DFCI/WUSTL[22]	RB/RC ×3 + ASCT	97%/90%	92% (3 years)	83% (3 years)	100%[2]

ASCT, autologous stem cell transplant; CR, complete response; DFCI/WUSTL, Dana-Farber Cancer Institute/Washington University in St Louis; HiDAC, high-dose cytarabine; maxi-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; MCL, mantle cell lymphoma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RB/RC, rituximab/bendamustine and rituximab/cytarabine; R-CHOP/RDHAP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone/ rituximab, dexamethasone, high-dose cytarabine, cisplatin.
0/15 samples found to have MRD positivity after 3 months of ASCT. 2/17 patients relapsed with post-ASCT samples. MRD positivity detected in one of the two patients that relapsed. MRD analysis using Ig-NGS with clonoSEQ™ (Adaptive Biotechnologies) was assessed in the DFCI trial.
[1]Should be after MRD negativity, and begin with "MRD analysis".
[2]Should be after 100% and being with "0/15 samples".

feasible strategy in relapsed and refractory MCL. In this review, we summarize the treatment landscape of newly diagnosed as well as relapsed and refractory MCL. We will then review the existing data regarding CAR T-cell treatment of MCL, focusing on brexucabtagene autoleucel (brexucel, formerly KTE-X19), which is approved for use in relapsed and refractory patients.

Management strategies of newly diagnosed MCL

Initial management of MCL management varies based on age and comorbidities. For the younger, fit population, patients receive induction with chemotherapy regimens containing high-dose cytarabine followed by consolidation with autologous stem cell transplant (ASCT). Less-intensive chemotherapy and maintenance rituximab therapy are considered for older patients and those with poor functional status.

Intensive therapy followed by ASCT

Intensive immunochemotherapy followed by consolidation with ASCT is the considered the current standard for young, fit, symptomatic patients with MCL. Consolidation with ASCT improves the duration of response.[18,19]

There are several highly efficacious induction regimens for younger MCL patients that incorporate high-dose cytarabine. These regimens include the Nordic regimen comprised of augmented-strength cyclophosphamide, doxorubicin, vincristine, and prednisone (maxi-CHOP) alternating with high-dose cytarabine and rituximab, R-CHOP alternating with rituximab, dexamethasone, cytarabine and a platinum-derivative (R-DHAP), and rituximab and bendamustine (RB) either alternating or sequentially given with rituximab and high-dose cytarabine (RC).[20–22] Table 1 provides details of these regimens. Rituximab maintenance has additionally shown an overall survival (OS) benefit following ASCT.[23]

The role of transplant is undergoing reevaluation in certain groups. The ongoing ECOG-ACRIN 4151 study aims to determine the necessity of ASCT patients who are minimal residual disease (MRD) negative status as determined by next-generation sequencing (NGS), given the excellent outcomes in these patients. The results of this trial could determine whether a consolidative ASCT is needed in this group.

Despite the excellent outcomes in most young patients, there are high-risk groups that do not derive much benefit from intensive therapy. A high Ki-67 proliferation index above 30% is associated with shortened OS rates and progression-free survival (PFS).[24] In young patients with aggressive MCL disease, the presence of *TP53* mutations correlates with poor response to conventional intensive induction therapy and ASCT, with poor OS.[5] Novel approaches are needed in these patients.

Table 2. Non-intensive treatment approaches of MCL.

Trial, regimen		ORR/CR	OS rate	PFS	MRD negativity
StiL study[25]	B-R	93%/40%	67.4% (10 years)	NR for MCL (69.5 months for all subtypes)	N/A
BRIGHT Study[27,30]	B-R *versus* R-CHOP/R-CVP	97%/31%, *91%/25%*	81.7%, *85.0%*, HR: 0.86*	65.5%, *55.8%*, (5 years), HR: 0.40**	N/A
Ruan *et al.*[29,31]	Lenalidomide and rituximab	92%/64%	82.6% (4 years)	70% (4 years, est.)	86%***
Robak *et al.*[32]	Bortezomib (VR-CAP)	92%/53%	Median NR, 64% (4 years)	24.7 months	N/A

B-R, bendamustine plus rituximab; CR, complete response; HR, hazard ratio; MCL, mantle cell lymphoma; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone; Stil NHL1, study group of indolent lymphomas non-hodgkin lymphoma; VR-CAP, bortezomib plus rituximab, cyclophosphamide, doxorubicin, and prednisone.
*Hazard ratio (HR) for overall survival in mantle cell lymphoma (MCL) subgroup, (*p* = .6894).
**In favor of B-R for MCL subgroup (*p* = .0035).
***MRD was assessed using clonoSEQ (Adaptive Biotechnologies, Seattle WA) on subjects with available pre and post samples.

Non-intensive therapy

Older patients, or those with comorbid conditions are not able to tolerate intensive induction with high-dose cytarabine. Regimens such as bendamustine and rituximab or bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) are preferred treatments given randomized data comparing them to R-CHOP.[25–28] Lenalidomide and rituximab can also be considered in untreated patients who are not eligible for intensive induction.[29] Table 2 summarizes non-intensive treatment approaches.

There are some patients who present with indolent disease. MCL patients with indolent courses tend to have SOX11 negativity and *IGHV* mutations.[33] A multicenter trial conducted in the United Kingdom demonstrated that a proportion of patients with indicators of low disease burden are appropriate candidates for a conservative approach and observation.[34]

Relapsed and refractory disease MCL: current practices and unmet needs
In contrast to frontline treatment, chemoimmunotherapy has little role in the treatment of relapse and refractory patients. Targeted agents are predominantly used, given their safety and efficacy. Bortezomib,[35] temsirolimus,[36] and lenalidomide[9]

were the initial targeted treatments to receive regulatory approval; however, inhibitors of BTK have become the most important agents in second-line therapy. These targeted treatments are summarized in Table 3.

The introduction of BTK inhibitors has created a paradigm shift in the treatment of relapsed and refractory MCL. BTK is an essential enzyme for B-cell receptor signaling, is necessary for the activation of NF-kB pathway, and inhibition of the BTK pathway can negatively affect B-cell survival.[39] To date, the US Food and Drug Administration (FDA) has approved three BTK inhibitors for use in relapsed/refractory MCL including ibrutinib, acalabrutinib, and zanubrutinib. These agents covalently bond to cysteine in the BTK enzyme, causing irreversible inhibition, which allows for convenient dosing despite their short half-lives.[40] Given their efficacy and tolerability, we favor BTK inhibitor therapy at the time of first relapse outside of a clinical trial.

Ibrutinib, the first in class BTK inhibitor demonstrated efficacy as a single agent for in patients relapsed or refractory MCL who were heavily pretreated.[41,42] The responses were fairly durable and when compared to temsirolimus in a randomized phase-3 trial, ibrutinib showed better tolerability and superior PFS.[43]

Table 3. Approved targeted treatments in relapsed MCL.

Agent, class		ORR/CR	Median OS	PFS
Ibrutinib[10]	BTKi	64%/15%	35.1 months	27.4 months
Acalabrutinib[8]	BTKi	81%/40%	12 month OS rate 87%	67% (12 month)
Zanubritinib[37]	BTKi	87%/69%	12 month OS rate 84%	22.1 months
Lenalidomide[9]	Immunomodulator	53%/20%	4 year OS rate 81%	5.6 months
Temsirolimus (and rituximab)[38]	mTOR	59%/19%	29.5 months	6.2 months

BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; mTOR, mammalian target of rapamycin inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor.

Acalabrutinib (ACP-196) and zanubrutinib are second-generation BTK inhibitors that offer increased specificity compared to ibrutinib. While both agents target BTK, acalabrutinib and zanubrutinib only minimally target interleukin 2–inducible T-cell kinase (ITK), and does not target epidermal growth factor receptor (EGFR).[44,45]

The CR rates and durability of response in the studies with acalabrutinib and zanubrutinib compare favorably with ibrutinib; however, patients were somewhat less heavily pretreated.[8,37,46] Details regarding responses are included in Table 3.

While acalabrutinib and zanubrutinib have increased specificity to BTK and less off-target effects compared to ibrutinib, they have not been directly compared in terms of their safety profiles when used in MCL. Adverse events (AEs) reported with all BTKi commonly include hematologic toxicities, infections, and gastrointestinal side effects. Individually, ibrutinib caused diarrhea (54%), likely a result of EGFR inhibition, fatigue (50%) and nausea (33%), and neutropenia in 17% of patients.[47] In the trial assessing acalabrutinib, side effects also included diarrhea (31%), fatigue (27%), and neutropenia (10%).[8] The ASPEN trial compared zanubrutinib's efficacy and safety to ibrutinib, albeit in patients with Waldenstrom's macrolobulinemia (WM). Diarrhea, pneumonia, and cardiovascular toxicity (namely atrial fibrillation) were found to be less in zanabrutinib compared to ibrutinib.[48]

Patients who relapse after BTK inhibitor therapy are a high-risk clinical group, and effective therapy for these patients is an unmet clinical need. Initial retrospective data in patients progressing after ibrutinib described a dismal prognosis with a median OS of 2.9 months, though in a less heavily pretreated population randomized between ibrutinib and temsirolimus, patients had more favorable responses to subsequent treatment.[43,49,50] The optimal treatment of patients with progression following a BTK inhibitor is not well defined, but considerations include chemoimmunotherapy, venetoclax, and CAR T-cell therapy.

In a retrospective review, MCL patients who had progressed after BTKi therapy showed high ORR (83%) with the rituximab, bendamustine, and cytarabine (R-BAC) regimen. Although responses were not highly durable (median PFS 10.1 months), the R-BAC protocol served as a bridging strategy in transplant-eligible patients before consolidation with allogenic stem cell transplant (allo-SCT). Four patients that received R-BAC induction and allo-SCT consolidation had a response that exceeded 12 months.[51]

Another therapeutic class of interest in MCL is the BCL2 inhibitors. Venetoclax is a potent and selective BCL2 inhibitor, rendering it effective in multiple types of NHL, including MCL, where BCL2 is frequently overexpressed. In a phase-1 trial studying venetoclax in relapsed and refractory NHL, of the 28 MCL patients, the response rate was 75% (21 patients) and CR was achieved in 21%. Median PFS for MCL patients was 14 months. For MCL, the recommended dose of venetoclax needed to achieve a durable response while minimizing toxicity was 800 mg daily.[52]

Despite promising response rates, use of BTK and BCL2 inhibitors can be limited by the emergence

of drug resistance. While mutations in *BTK* and *PLCG2* (a kinase downstream from BTK) are associated with acquired ibrutinib resistance in patients with CLL, they are rarely seen in MCL patients with ibrutinib resistance.[53] There is evidence that acquired resistance to venetoclax in MCL be associated with mutations in *BCL2* family proteins.[54,55] Combination therapy is also actively being studied in relapsed and refractory MCL. Ibrutinib and venetoclax is a highly active combination, achieving outcomes to superior to that of each alone, with an acceptable safety profile. The synergistic effect of the inhibition of both the BTK pathway and BCL2 gene resulted in substantial response rates, with a CR of 42% and 62% at 16 weeks when assessed without a PET and with PET, respectively.[56] The ongoing phase-3 trial SYMPATICO (NCT03112174) is investigating the superiority of the ibrutinib and venetoclax combination compared to the use of ibrutinib alone in relapsed and refractory MCL.[7]

Role of allogenic stem cell transplant

Allogenic stem cell transplant (allo-SCT) in MCL is not a widely used strategy of MCL treatment due to the high non-relapse-related mortality (NRM) of 10% to 24%, even in the context of reduced intensity conditioning (RIC) regimens.[57] A prospective trial assessed allo-SCT as a salvage therapy for relapsed/refractory and as primary therapy for MCL which showed a 5-year OS of 73% and comparable outcomes in both groups. MRD analyses, assessed by quantitative polymerase chain reaction (PCR), was negative in 9/11 patients after allo-SCT from initial peripheral-blood samples.[58] A trial of 25 patients of allo-SCT does indicate that young patients with high-risk profiles, particularly *TP53* mutations, may benefit from an early allo-SCT.[59]

CAR T-cell therapy for relapsed/refractory B-cell lymphomas

For refractory B-cell lymphomas, adoptive cellular immunotherapy with CAR T-cells offers effective and durable clinical responses for a subset of patients. There are now four anti-CD19 CAR T-cells that are approved in B-cell lymphomas. This includes axicabtagene ciloleucel (axi-cel) for diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, tisagenlecleucel (tisa-cel) for DLBCL, lisocabtagene maraleucel (liso-cel)

for DLBCL, and brexucabtagene autoleucel (brexu-cel) for MCL. Key components of the CAR are crucial to the antitumor activity. The single-chain variable fragment binds to the target antigen on a tumor cell, and in the case of B-cell lymphomas, these specifically target B-lineage cells independent of the major histocompatibility complex. The endodomain of the currently available CARs include the CD3ζ subunit for cell signaling and either CD28 or 4-1BB to provide a costimulatory signal.

Most of the lymphoma experience with anti-CD19 CAR T-cells is with DLBCL patients. Early experiences were limited to relatively small, single institutional trials.[60,61] More recently, multicenter trials of CAR T-cells have led to approval of various CAR-T products by regulatory agencies. Axicabtagene ciloleucel (Axi-cel; formerly KTE-C19) is an anti-CD19 CAR-T-cell product approved as a third-line (or higher) therapy for relapsed and refractory large B-Cell lymphomas (LBCL) including diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma (HGBCL), and transformed follicular lymphoma (tFL). This autologous therapy was approved for refractory LBCL by the FDA in 2017 and shortly after in 2018 by the European Medical Agency (EMA) based on promising phase-2 data from the ZUMA-1 trial that showed long-term remission and complete response rates. Among the 108 patients in the updated analysis of the phase-1 and -2 portions of the trial, after a 1-year follow-up, ORR and CR was 82% and 58%, respectively and the median DOR was 11 months.[13,62] The second anti-CD19 CAR product for lymphoma, tisagenlecleucel (tisa-cel; CTL019) was also approved in 2017 for use in relapsed and refractory DLBCL based on results of the international, phase-2, pivotal JULIET trial.[63] In the JULIET trial, 93 patients received tisa-cel and were evaluated for efficacy and safety. The primary endpoint, best ORR was 52% (40% CR). Relapse-free survival at 12 months was estimated to be 65%.[15]

Anti-CD19 CAR agent Lisocabtagene maraleucel (Liso-cel; formerly JCAR017) was investigated in the TRANSCEND trial for treatment of LBCLs. Among the 255 patients evaluated for efficacy in TRANSCEND, ORR was 73%; the CR rate was 53%. At 12 months, DOR and PFS was 55% and 44%, respectively.[64]

Table 4. Grading of cytokine release syndrome.

	Symptom severity	Oxygen requirement	Hypotension	Organ toxicity
Grade 1	• Symptoms are not life threatening • Require symptomatic treatment only (ex. fever, nausea, headache, myalgias, and malaise)			
Grade 2	Require and respond to moderate intervention	Oxygen requirement <40% OR	Responsive to fluids or low dose of one vasopressor OR	Grade-2 organ toxicity
Grade 3	Require and respond to aggressive intervention	Oxygen requirement >40% OR	Requiring high dose or multiple vasopressors OR	Grade 3 organ toxicity or grade-4 transaminitis
Grade 4	Life-threatening symptoms	Requirement for ventilator support OR		Grade-4 organ toxicity (excluding transaminitis)

Adapted from Lee *et al.*[67]

Toxicity

Toxicities of particular interested in CAR T-cell treatment are cytokine-associated toxicity, also known as cytokine release syndrome (CRS), neurotoxicity, and hematologic toxicity. CRS is a toxicity resulting from the *in vivo* expansion of CAR-T-cells which cause a systemic inflammatory response characterized by the release of multiple cytokines. Various grading systems have been developed to grade CRS severity including versions of the Common Terminology Criteria for Adverse Events (CTCAE), Penn Criteria, American Society for Transplantation and Cellular Therapy (ASTCT), CAR-T-cell therapy–associated TOXicity (CARTOX) and Lee criteria. The Lee criteria have been widely used in CAR-T-cell clinical trials (Table 4).[65–69] Symptoms range from mild constitutional symptoms to severe life-threatening manifestations resulting in organ toxicity. Grade-1 CRS is generally managed with supportive measures. In higher grades of CRS, tocilizumab, an anti-IL-6 receptor antibody, as well as glucocorticoids are used for treatment. Glucocorticoids and supportive care are the mainstays of treatment for higher grades of CRS and neurotoxicity.

Neurotoxicity, defined in this context as immune effector cell–associated neurotoxicity syndrome (ICANS), by the ASTCT, can manifest as delirium, encephalopathy, lethargy, tremor, seizures, agitation and rarely, cerebral edema. An ICANS score is graded using the 10-point immune effector cell encephalopathy (ICE) score, which assess mental status through a short series of questions related to orientation, naming, following commands, attention, and writing.[69]

A comparison of rates of AEs of grade 3 from major CAR-T trials is reviewed in Table 5.

CAR T-cells for the treatment of relapsed and refractory MCL

The experience with CAR-T-cells in MCL is more limited. Recently, however, there are two trials that showed intriguing results in relapsed and refractory MCL patients. One of these studies, ZUMA-2, led to FDA approval of brexucabtagene autoleucel (brexu-cel). The TRANSCEND NHL 001 study included a dose expansion cohort of relapsed and refractory MCL patients treated with liso-cel, and these data have now been presented in abstract form. We will review these studies including details of the CAR T-cells used, study populations, safety and efficacy data.

The phase-2 ZUMA-2 trial investigated the role of brexucabtagene autoleucel (brexu-cel) for patients with relapsed and refractory MCL and is the first multicenter clinical trial of CAR-T-cells in this population. The study population was comprised of patients who had received two or more prior lines of therapy, one of which had to include either ibrutinib or acalabrutinib, which

Table 5. Comparing structure, LDC regimen, and toxicity profiles of grade ⩾3 adverse events with various CAR-T therapies.

PRODUCT, TRIAL	Costimulatory subunit	LDC regimen	Adverse event (grade ⩾3)	Grade ⩾3 CRS	Grade ⩾3 ICANS	Grade ⩾3 cytopenia
Axi-cel, ZUMA-1[13,62]	CD28	Flu/Cy ×3d	96%	13%	28%	Neutropenia, 78%
Tisa-cel, JULIET[15]	4-1BB	Bendamustine or Flu/Cy ×3d	85%	22%	12%	32%
Liso-cel, TRANSCEND[64]	4-1BB	Flu/Cy ×3d	79%	2%	10%	Neutropenia, 60%
Brexu-cel, ZUMA-2[16]	CD28	Flu/Cy ×3d	99%	15%	31%	94%

d, days; Flu/Cy, fludarabine/cyclophosphamide; LDC, lymphodepleting chemotherapy.

were the BTK inhibitors that were approved for use in MCL patients at the time.[16]

Brexu-cel is a second-generation CAR that contains an external single-chain variable fragment (scFv) domain, an intracellular CD28 costimulatory domain, and the CD3ζ signaling domain of the T-cell receptor. The external domain allows for the CAR-T-cell to target and bind to the CD19 antigen on B-cells and works in concert with the intracellular CD3ζ signaling domain to activate T-cell signaling and trigger a cascade of cytokine events that facilitate tumor destruction. CARs mediate apoptosis of tumor cells through the direct release of cytotoxic granules containing granzyme B and perforin.[70] Co-stimulation with CD28 is essential for improved CAR-T expansion, persistence, and antitumor activity.[71]

The CAR design of brexu-cel is the same as axi-cel, but there are important differences in the manufacturing process. With both products, autologous peripheral-blood mononuclear cells are collected with leukapheresis and transported to the manufacturing facility. For brexu-cel, a T-cell-enrichment step is necessary as patients with acute lymphoblastic lymphoma and MCL have leukemic blasts or lymphoma cells present in the autologous product. T-cell enrichment is performed with the use of magnetic beads that are coated with ant-CD4 and anti-CD8 antibodies.[72] The product is then cultured in IL-2 followed by transduction of the CAR gene with a lentiviral vector. The CAR-T product is harvested and undergo quality assurance testing prior to release. There is no selection of specific T-cell subsets for the final product with either brexu-cel or axi-cel.[73,74]

On ZUMA-2 patients received a single intravenous infusion of brexu-cel at a dose of 2×10^6 cells per kilogram of body weight on day 0 following lymphodepletion. The dose of brexu-cel was chosen based on the dose of axi-cel given to patients with DLBCL on the ZUMA-1 trial. Treatment with brexu-cel was feasible in this high-risk population and was successfully manufactured in approximately 95% of patients. Three additional patients did not receive brexu-cel due to progressive disease or ineligibility.[16]

In the cohort used for the primary efficacy analysis ($n=60$), brexu-cel was highly active with an ORR of 93% with 67% achieving a CR. The ORR was 85% with 59% achieving a CR in all 74 subjects enrolled in an intention-to-treat analysis. Responses to therapy were rapid with brexu-cel with a median time to achieve response of 1 month, and median time to achieve CR of 3 months. There was evidence that responses deepened over time with over half of patients who initially had a PR or stable disease developing a CR with longer follow-up. Considerable depth of response at early timepoints was seen in patients treated with brexu-cel. MRD by the clonoSEQ assay at a level of 10^{-6} in peripheral-blood mononuclear cells was performed in a subset of patients, and 83% of the patients analyzed had no detectable disease by 4 weeks.[16]

Responses to brexu-cel have been durable with longer follow-up. With a median follow-up of 17.5 months, 48% of patients in the primary analysis remained in response, and the median PFS and OS have not been reached. There is even longer follow-up for the first 28 patients dosed on the trial. Thirty-nine percent of these patients

remain in response with 32.3 months of follow-up.[75] The long-term durability of brexu-cel is not yet known, but its activity to date in a high-risk population of BTK inhibitor refractory patients is encouraging.

Objective response, PFS, and OS were similar among various subgroups, including those with high Ki-67 index (cutoff above 50%), *TP53* mutations, and pleomorphic morphology.[76] When stratified by age, patients younger than 65 had similar ORR compared to their older counterparts, at 93% and 94%, respectively. Patients with high MIPI assessment scores also had similar ORR (94%) to those with low risk (92%). LDH levels, extranodal disease, and bone marrow involvement also did not significantly alter response to brexu-cel. Exposure to bridging therapy (such as steroids or BTK inhibitors) was not a factor affecting response rates to therapy with brexu-cel.[16]

All patients treated with KTE-X19 had at least one AE, and 99% of the patients had an AE of grade 3 or higher. Hematologic toxicity was the most common AE, with grade-3 toxicity seen in 94% of patients. Infections were also fairly common, and grade 3 or greater infections occurred in about a third (32%) of patients.[16] Two patients (3%) had grade-5 AEs, both infectious in nature and related to conditioning chemotherapy, although in the latter patient, the bacteremia that was attributed to brexu-cel infusion in addition to chemotherapy.

As with all CAR-T-cell products, CRS and ICANS are AEs of particular interest. CRS grading in ZUMA-2 was adapted from Lee *et al.* (Table 4) and neurologic events (NEs) were classified per the NCI's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[67,77]

A total of 91% of patients experienced any grade of CRS, with 15% grade 3 or greater. There were no grade-5 events related to CRS. To manage CRS, tocilizumab was administered in 59% of all treated patients. Twenty-two percent of patients received glucocorticoids for management of CRS.

NEs occurred in a total of 63% (43) of patients and 31% of patients had events that were grade 3 or higher. No deaths occurred as a result of NE, although one patient did experience cerebral edema but made a full recovery following surgical decompression and antithymocyte globulin.

Tocilizumab was administered in 26% of all patients for management of NEs, and 38% received glucocorticoids.[16]

Given that brexu-cel specifically targets CD19-positive cells, B-cell aplasia is an expected side effect. The primary risk of B-cell aplasia is the potential for infections secondary to the resulting hypogammaglobulinemia. Thirty-two percent of patients receive intravenous immunoglobulin infusions. All patients who had an objective response and successful CAR-T-cell expansion demonstrated B-cell aplasia by flow cytometry on the first assessment. In contrast, all patients who did not have a response did not have B-cell aplasia during the trial.[16] With longer follow-up, patients with ongoing responses at 12 months have demonstrated evidence of B-cell recovery.[75]

Higher CAR-T-cell expansion was seen in patients who had grade ≥3 CRS and NE compared to patients who experienced grade 2 or lower events. Tocilizumab was thus indirectly reflective of higher CART expansion, as its use is reserved for occurrence of high-grade events. Tocilizumab administration was also associated with higher area under the curve (AUC) and peak levels, regardless of whether glucocorticoids were concurrently used.

While increased CAR-T-cell expansion is associated with more severe CRS and ICANS, it is also predictive of response, as both the AUC and peak levels were found to be much higher in patients who responded to therapy and did not have MRD by the assessment at week 4. Although tocilizumab was associated with higher response to therapy, it correlated with a PFS rate of 74% at 6 months, comparable to the 83% PFS in those who did not receive tocilizumab.[16]

The data with other CAR-T-cells in MCL are not as mature, but available data for lisocabtagene maraleucel (liso-cel) are suggestive of high clinical activity. Liso-cel is a second-generation, anti-CD19 CAR T-cell with a 4-1BB costimulatory subunit. In contrast to brexu-cel, the manufacturing of liso-cel is designed to produce a final product that is a 1:1 ratio of CD4:CD8-positive CAR-T-cells. Following collection the CD4 and CD8 positive T-cells are magnetically sorted and manufactured independently. This includes the activation, viral transduction, expansion, and cryopreservation. Cells are thawed and administered as

sequential infusions following lymphodepletion with fludarabine and cyclophosphamide.[78] In murine models, using a defined ratio of CD4:CD8-positive T-cells resulted in improved efficacy of the product.[79]

The TRANSCEND study enrolled patients with multiple different subtypes of lymphoma, including MCL. As of December 2020, 41 patients underwent collection and 32 patients were infused with liso-cel. In patients who were dosed with liso-cel, it was highly active with an ORR of 84% and 59% achieved a CR. The investigators also reported that the patients with blastoid morphology had a response rate of 75%.[80]

Liso-cel demonstrated excellent safety in this population. Hematologic toxicities were the most common grade 3 and greater AEs. Thirty-four percent of patients had grade 3 or greater hematologic toxicity that persisted past day 29 postinfusion.[80]

Severe CRS or ICANS were uncommon with this product. Fifty percent of patients had any grade CRS, but only 3% had a grade 3 or greater event. Twenty-eight percent of patients had NEs with 9% of these events grade 3 or greater. Thirty-one percent of patients received tocilizumab and/or corticosteroids for management of CRS or ICANS.[80]

Future directions
Targeted therapy with the approved BTK inhibitors, ibrutinib, acalabrutinib, and zanubrutinib have changed the landscape in the treatment of relapsed and refractory MCL. Second-generation BTKi agents are under development with recently reported phase-1 results for tirabrutinib (ONO-4059/GS-4059) and phase-2 outcomes for orela-brutinib (ICP-022). These and other agents may soon become emerging treatment options for MCL.[81,82] As previously discussed, the combination of venetoclax and ibrutinib offered substantial response and activity. Results from trials such as phase-3 SYMPATICO comparing the efficacy of the combination of these two agents *versus* monotherapy ibrutinib may be able to answer whether this is truly the superior approach.[7] The appropriate sequencing of agents in the relapsed and refractory patient and the optimal use of CAR-T-cells in MCL are not yet defined, given the limited nature of the available data.

In ZUMA-2, the median number of prior lines of therapy was four, but this ranged to as high as 10 previous therapies.[16] In TRANSCEND, MCL patient were similarly heavily pretreated with a median three prior lines of therapy with a range up to seven.[80] The use of CAR-T-cells earlier in the course of disease is an important area of future research, especially in high-risk patients who derive little benefit from chemoimmunotherapy. In addition, there are other novel CAR T-cell products that will be studied in MCL.

As with targeted agents discussed above, rational combinations with CAR T-cells should be considered. There is preliminary evidence of CAR-T therapy synergism with ibrutinib in a preclinical study using mouse xenograft models of MCL, the addition of ibrutinib to CTL019 enhanced the preexisting potency of the antitumor CAR-T-cell function.[83]

Conclusion
Despite multiple advancements, MCL remains an incurable disease. Future directions in the treatment of MCL are moving toward utilizing combinations of different targeted agents such as the concurrent inhibition of BTK, BCL2, and targeting of CD19. As CAR-T therapies become standard in the treatment of relapsed and refractory lymphomas, brexu-cel and liso-cel are also proving efficacious in relapsed and refractory MCL. The efficacy of CAR-T-cells even in high-risk subgroups may point toward its utility earlier in the course of their management. In relapsed and refractory MCL, brexu-cel provides high rates of response with a tolerable safety profile. Stratifying patients according to their level of risk, such as the presence of high-risk *TP53* mutations and elevated Ki-67 index, may be useful in individualizing the approach of MCL patients.

Author contributions
Bushra Tbakhi: Conceptualization; Visualization; Writing – original draft; Writing – review & editing.

Patrick M Reagan: Conceptualization; Supervision; Writing – review & editing.

Conflict of interest statement
The authors declared the following potential conflicts of interest with respect to the research,

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